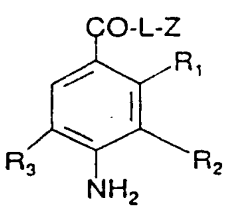




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/GB91/02210 <b>(22) International Filing Date:</b> 12 December 1991 (12.12.91)  <b>(30) Priority data:</b> 9027487.9                      19 December 1990 (19.12.90) GB  <b>(71) Applicant (for all designated States except US):</b> BEECHAM GROUP PLC [GB/GB]; Four New Horizons Court, Harlequin Avenue, Brentford, Middlesex TW8 9EP (GB).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only) :</b> KING, Francis, David [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).		<b>(74) Agent:</b> JONES, Pauline; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).  <b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> AZABICYCLIC AMIDES OR ESTERS OF HALOGENATED BENZOIC ACIDS  <div style="text-align: center;">  <p>(I)</p> </div> <b>(57) Abstract</b> <p>Compounds of formula (I) wherein Z is a di-azacyclic or azabicyclic side chain having 5-HT<sub>3</sub> receptor antagonist activity.</p>		

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## AZABICYCLIC AMIDES OR ESTERS OF HALOGENATED BENZOIC ACIDS

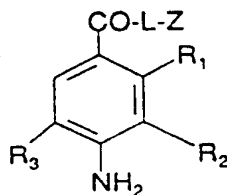
This invention relates to novel compounds having pharmacological activity, to a process for their preparation and their use as pharmaceuticals.

EP-A-220011 (Beecham Group p.l.c.) describes the use of a benzamide derivative, as a 5-HT<sub>3</sub> receptor antagonist.

10 A group of novel compounds has now been discovered, which compounds are 5-HT<sub>3</sub> receptor antagonists.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:

15



20

(I)

wherein

R<sub>1</sub> is hydrogen or C<sub>1-6</sub> alkoxy;

25 R<sub>2</sub> is halo;

R<sub>3</sub> is halo;

L is O or NH; and

Z is a di-azacyclic or azabicyclic side chain; having 5-HT<sub>3</sub> receptor antagonist activity.

30

Suitable examples of alkyl moieties in R<sub>1</sub> include methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl.

Suitable examples of halo moieties include fluoro, chloro and bromo.

5 In particular,  $R_1$  is hydrogen,  $R_2$  is chloro and  $R_3$  is chloro; or  $R_1$  is methoxy,  $R_2$  is fluoro or chloro and  $R_3$  is chloro.

Suitable examples of Z are described in the art relating to  
10 5-HT<sub>3</sub> receptor antagonists, ie. as follows:

- i) GB 2125398A (Sandoz Limited)
- ii) GB 2152049A (Sandoz Limited)
- iii) EP-A-215545 (Beecham Group p.l.c.)
- 15 iv) EP-A-214772 (Beecham Group p.l.c.)
- v) EP-A-377967 (Beecham Group p.l.c.)
- vi) PCT/GB91/01629 (Beecham Group p.l.c.)
- vii) EP-A-358903 (Dianippon)

20 Particular side chains of interest are depicted thus:

Tropane

25



Granatane

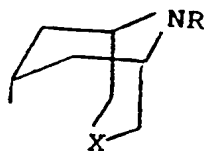
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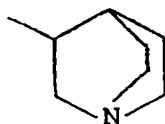
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Oxa/thia-granatane

5

Quinuclidine

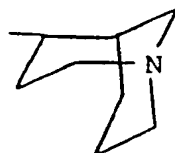
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15 Isoquinuclidine

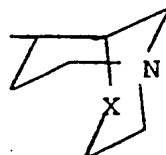
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Isogranatane

25

Oxa/thia-isogranatane

30



Isotropane

5



or



wherein

R is hydrogen or methyl; and X is oxygen, sulphur or  
10 nitrogen optionally substituted by C<sub>1-6</sub> alkyl, C<sub>3-8</sub>  
cycloalkyl, C<sub>3-8</sub> cycloalkyl C<sub>1-4</sub> alkyl, phenyl, naphthyl,  
phenyl C<sub>1-4</sub> alkyl or naphthyl C<sub>1-4</sub> alkyl wherein a phenyl or  
naphthyl moiety is optionally substituted by one or more of  
halo, C<sub>1-6</sub> alkoxy or C<sub>1-6</sub> alkyl.

15

Side chains Z of particular interest include tropane,  
oxagranatane and azagranatane, where R is methyl. Suitable  
values for N-substituents when X is N are as described in  
PCT/GB91/01629, for example, iso-propyl or ethyl.

20

L is preferably NH.

Alternatively, COL in formula (I) may be replaced by a  
bioisostere therefor, for example, 1,2,4-oxadiazole and the  
25 other groups of structure h) described in EP-A-377967  
(Beecham Group p.l.c.).

The pharmaceutically acceptable salts of the compounds of  
the formula (I) include acid addition salts with  
30 conventional acids such as hydrochloric, hydrobromic, boric,  
phosphoric, sulphuric acids and pharmaceutically acceptable  
organic acids such as acetic, tartaric, maleic, citric,  
succinic, benzoic, ascorbic, methanesulphonic,  $\alpha$ -keto  
glutaric,  $\alpha$ -glycerophosphoric, and glucose-1-phosphoric  
35 acids.

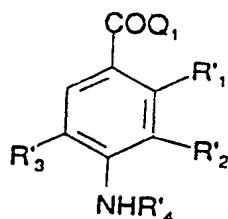
Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds  $R_X-T$  wherein  $R_X$  is  $C_{1-6}$  alkyl, phenyl- $C_{1-6}$  alkyl or  $C_{5-7}$  cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of  $R_X$  include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

- 10 Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and  
15 N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

- 20 It will of course be realised that some of the compounds of the formula (I) have chiral or prochiral centres and thus are capable of existing in a number of stereoisomeric forms including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to  
25 mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

The invention also provides a process for the preparation of  
30 a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):



(II)

with a compound of formula (III):

HLZ'

(III)

5 or a reactive derivative thereof, when L is O;

wherein  $R_1'$ ,  $R_2'$ ,  $R_3'$  and/or  $Z'$  are  $R_1$ ,  $R_2$ ,  $R_3$  and/or  $Z$  respectively or groups or atoms convertible thereto;  $R_4$  is hydrogen or an N-protecting group;  $Q_1$  is a leaving group;  
10 and the remaining variables are as hereinbefore defined; and thereafter optionally converting  $R_1'$ ,  $R_2'$ ,  $R_3'$  and/or  $Z'$  to another group or atom  $R_1$ ,  $R_2$ ,  $R_3$  or  $Z$ ; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

15

Examples of  $R_4$ , when other than hydrogen, include  $C_{1-10}$  acyl such as  $C_{1-7}$  alkanoyl, wherein the alkyl may be as listed for  $R_1$ , preferably acetyl.

$R_4$  is usually hydrogen.

20

Examples of leaving groups  $Q_1$ , displaceable by a nucleophile, include halogen such as chloro and bromo, hydroxy,  $C_{1-4}$  alkoxy, such as  $CH_3O$  and  $C_2H_5O$ -,  $PhO$ -, activated hydrocarbyloxy, such as  $Cl_5C_6O$ - or  $Cl_3CO$ -; or  
25  $COQ_1$ , forms a mixed anhydride, so that  $Q_1$  is carboxylic acyloxy; or a nitrogen-linked heterocycle, such as imidazole.

If a group  $Q_1$  is a halide, or  $COQ_1$ , forms a mixed anhydride,  
30 then the reaction is preferably carried out at non-extreme temperatures in an inert non-hydroxylic solvent, such as benzene, dichloromethane, toluene, diethyl ether, tetrahydrofuran (THF) or dimethylformamide (DMF). It is also preferably carried out in the presence of an acid  
35 acceptor, such as an organic base, in particular a tertiary amine, such as triethylamine, trimethylamine, pyridine or



-7-

picoline, some of which can also function as the solvent. Alternatively, the acid acceptor can be inorganic, such as calcium carbonate, sodium carbonate or potassium carbonate. Temperatures of 0°-100°C, in particular 10-80°C are  
5 suitable.

If a group  $Q_1$  is  $C_{1-4}$  alkoxy, phenoxy or activated hydrocarbyloxy then the reaction is preferably carried out in an inert polar solvent, such as toluene or  
10 dimethylformamide. It is also preferred that the group  $Q_1$  is  $Cl_3CO-$  and that the reaction is carried out in toluene at reflux temperature.

If a group  $Q_1$  is hydroxy, then the reaction is generally  
15 carried out in an inert non-hydroxylic solvent, such as dichloromethane, THF or DMF optionally in the presence of a dehydrating agent such as a carbodiimide, for example dicyclohexylcarbodiimide. The reaction may be carried out at any non-extreme temperature, such as -10 to 100°C, for  
20 example, 0 to 80°C. Generally, higher reaction temperatures are employed with less active compounds whereas lower temperatures are employed with the more active compounds.

If a group  $Q_1$  is carboxylic acyloxy, then the reaction is  
25 preferably carried in substantially the same manner as the reaction when  $Q_1$  is halide. Suitable examples of acyloxy leaving groups include  $C_{1-4}$  alkanoyloxy and  $C_{1-4}$  alkoxycarbonyloxy, in which case the reaction is preferably carried out in an inert solvent, such as dichloromethane, at  
30 a non-extreme temperature for example ambient temperatures in the presence of an acid acceptor, such as triethylamine.  $C_{1-4}$  alkoxycarbonyloxy leaving groups may be generated in situ by treatment of the corresponding compound wherein  $Q_1$  is hydroxy with a  $C_{1-4}$  alkyl chloroformate.

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If a group  $Q_1$  is activated hydrocarbyloxy then the reaction is preferably carried out in an inert polar solvent, such as dimethylformamide. It is also preferred that the activated hydrocarbyloxy group is a pentachlorophenyl ester and that the reaction is carried out at ambient temperature.

When Y is O the compound of formula (III) may be in the form of a reactive derivative thereof, which is often a salt, such as the lithium, sodium or potassium salt.

10

An  $R_2'$  or  $R_3'$  group which is convertible  $R_2$  or  $R_3$  include a hydrogen substituent which is convertible to a halogen substituent by halogenation using conventional halogenating agents.

15

$Z'$  when other than Z may be wherein R is replaced by  $R'$  which is a hydrogenolysable protecting group which is benzyl optionally substituted by one or two groups selected from halo,  $C_{1-4}$  alkoxy and  $C_{1-4}$  alkyl. Such benzyl groups may, for example, be removed, when  $R_1/R_2$  is not halogen, by conventional transition metal catalysed hydrogenolysis to give compounds of the formula (I) wherein R is hydrogen.

This invention also provides a further process for the preparation of a compound of the formula (I) wherein R is methyl or a pharmaceutically acceptable salt thereof, which comprises N-methylating a compound of formula (I) wherein R is hydrogen, and optionally forming a pharmaceutically acceptable salt of the resulting compound of the formula (I). In this further process of the invention 'N-methylation' may be achieved by reaction with a compound  $CH_3Q_2$  wherein  $Q_2$  is a leaving group.

Suitable values for  $Q_2$  include groups displaced by nucleophils such as Cl, Br, I,  $OSO_2CH_3$  or  $OSO_2C_6H_4pCH_3$ ,

-9-

preferably Cl, Br or I.

The reaction may be carried out under conventional alkylation conditions for example in an inert solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate. Generally the reaction is carried out at non-extreme temperature such as at ambient or slightly above.

10 Alternatively, 'N-methylation' may be effected under conventional reductive alkylation conditions.

Interconverting R in the compound of the formula (III) before coupling with the compound of the formula (II) is also possible. Such interconversions are effected conveniently under the above conditions. It is desirable to protect any amine function with a group readily removable by acidolysis such as a C<sub>2-7</sub> alkanoyl group, before R/Z interconversion.

20

It is often convenient in the preparation of such a compound of formula (III) to prepare the corresponding compound wherein the methyl group is replaced by alkoxycarbonyl. Such compounds may then be reduced using a strong reductant such as lithium aluminium hydride to the corresponding compound of formula (II).

The benzoic acid derivative intermediates of formula (II) are known or are preparable analogously to, or routinely from, known compounds. When R<sub>2</sub> is fluoro, the intermediate may be prepared by fluorination of the corresponding R<sub>2</sub> is hydrogen compound, using a suitable fluorinating catalyst, such as trifluoromethyl hypofluorite, as described in Description 1 hereinafter.

35

Compounds of the formula (III) are generally prepared from the corresponding exocyclic keto derivative of the

-10-

azabicyclic side chain, prepared by condensation methods, often using a substituted piperidine. They may be prepared by processes described in the aforementioned Patent Publications relating to values of the side chain Z.

5

It will be realised that in the compounds of the formula (I) having a tropane, granatane or oxa/thia/aza-granatane side chain, the -COL- linkage has an **endo** orientation with respect to the ring of the bicyclic moiety to which it is  
10 attached. A mixture of **endo** and **exo** isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventionally therefrom e.g. by chromatography; or alternatively the **endo** isomer may if desired be synthesised from the corresponding **endo** form  
15 of the compound of the formula (II). Corresponding geometric isomeric pairs are possible for the isoquinuclidine, isogranatane, oxa/thia-isogranatane and isotropane side chains.

20 Pharmaceutically acceptable salts of the compounds of this invention may be formed conventionally.

The salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable  
25 organic or inorganic acid.

The compounds of the present invention are 5-HT<sub>3</sub> receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of pain, emesis, CNS disorders  
30 and gastrointestinal disorders. Pain includes migraine, cluster headache, trigeminal neuralgia and visceral pain; emesis, includes, in particular, that of preventing vomiting and nausea associated with cancer therapy, post-operative emesis, and nausea associated with migraine. Examples of  
35 such cancer therapy include that using cytotoxic agents, such as platinum complexes including cisplatin, and also

doxorubicin and cyclophosphamide, particularly cisplatin; and also radiation treatment. CNS disorders include anxiety, psychosis, cognitive disorders such as senile dementia and age associated memory impairment (AAMI), and 5 drug dependence. Gastrointestinal disorders include irritable bowel syndrome and diarrhoea.

5-HT<sub>3</sub> receptor antagonists may also be of potential use in the treatment of obesity, arrhythmia, and/or disorders 10 associated with myocardial instability.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable 15 carrier.

Such compositions are prepared by admixture and are usually adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid 20 preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

25 Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated 30 according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants 35 include starch, polyvinylpyrrolidone and starch

derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

30

The oral compositions may be prepared by conventional methods of blending, filling or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course,

conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing.

10 Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

15

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

30

An amount effective to treat the disorders herein- before described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal.

35 However, a unit dose for a 70kg adult will normally contain 0.05 to 1000mg for example 0.5 to 500mg, of the compound of the invention. Unit doses may be administered once or more

than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

5

No adverse toxicological effects are indicated within the aforementioned dosage ranges.

The invention also provides a compound of formula (I) or a  
10 pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of pain, emesis, CNS disorders and/or gastrointestinal disorders.

15 The following Examples illustrate the preparation of compounds of formula (I).

#### Examples

20

Ex. No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	L	Z
1	H	Cl	Cl	NH	NmT
2	H	Cl	Cl	NH	Q
25 3	OCH <sub>3</sub>	Cl	Cl	NH	NmT
4	OCH <sub>3</sub>	Cl	Cl	NH	NmO
5	OCH <sub>3</sub>	F	Cl	NH	NmT

30

NmT = N-methyltropane

Q = Quinuclidin-3-yl

NmO = N-methyloxagranatane



Descriptiona) Methyl-4-acetamido-5-chloro-3-fluoro-2-methoxybenzoate

5 Methyl-4-acetamido-5-chloro-2-methoxy benzoate (10.9g) was dissolved in chloroform (40 ml), cooled to -10°C under nitrogen. A three molar excess of trifluoromethyl hypofluorite was slowly bubbled through the stirred, cooled solution for 6 hours. A slow positive nitrogen stream was  
10 maintained throughout the reaction. After warming to room temperature and thoroughly purging with nitrogen, the chloroform was removed in vacuo.

The residue was chromatographed on silica using chloroform  
15 with increasing amounts of methanol as eluant. The product was isolated as an off white solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 250MHz

20 δ: 7.64 (d, 1H), 7.37 (bs, 1H), 3.98 (bs, 3H), 3.9 (s, 3H), 2.2 (s, 3H)

b) 4-Amino-5-chloro-3-fluoro-2-methoxybenzoic acid

25 Methyl-4-acetamido-5-chloro-3-fluoro-2-methoxybenzoate (1.89g) in 25 ml ethanol was treated with a solution of sodium hydroxide (1.15g) in 15 ml water. The mixture was heated under reflux for 16 hours then cooled. The solvent was removed in vacuo and the residue acidified. The  
30 precipitated solid was collected by filtration to give 1.48g product.

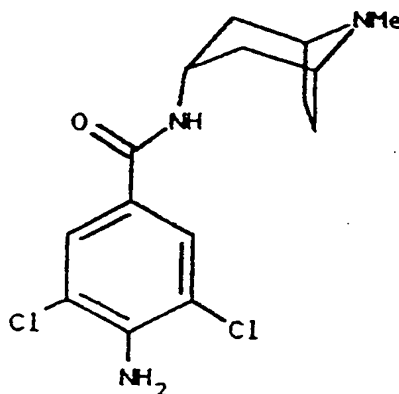
<sup>1</sup>H NMR (DMSO) 250MHz

35 δ: 7.49 (d, 1H), 6.19 (bs, 1H), 3.80 (s, 3H)

Example 1endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-amino-3,5-dichlorobenzamide (E1)

5

10



15 To a stirred solution of 4-amino-3,5-dichlorobenzoic acid (1.1g) in CH<sub>2</sub>Cl<sub>2</sub> (50 ml) and Et<sub>3</sub>N (0.8 ml) at 0°C was added EtO<sub>2</sub>CCl (0.48 ml). After stirring to room temperature for 1h, a solution of the **endo**-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (0.7 g) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was  
20 added and the whole stirred overnight. The reaction mixture was washed with sat. NaHCO<sub>3</sub> solution, dried and evaporated. Recrystallisation of the residue (EtoAc/petrol) gave the title compound (0.35 g) mp 192-193°C.

25

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.55 (s, 2H)

6.25 (brd 1H)

4.76 (brs, 2H)

4.22 (q, 1H)

3.21 (brs, 2H)

30

2.33 (s, 3H)

2.35-2.10 (m, 4H)

1.88-1.68 (m, 4H)

Prepared similarly was:

Example 2

5 N-(1-Azabicyclo[2.2.2]octan-3-yl)-4-amino-3,5-  
dichlorobenzamide (E2)

mp 233-235°C.

10

Example 3

endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-amino-3,5-  
dichloro-2-methoxybenzamide (E3)

15

A solution of endo-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-amino-5-chloro-2-methoxybenzamide (0.8g) in CH<sub>3</sub>COOH (25 mL) was treated with a solution of Cl<sub>2</sub> (0.18 g) in CH<sub>3</sub>COOH (5 mL). After standing at room temperature  
20 overnight, the solvent was removed by rotary evaporation and the residue partitioned between EtOAc and aqueous NaHCO<sub>3</sub> solution. The organic extract was separated, dried (K<sub>2</sub>CO<sub>3</sub>) evaporated and the residue purified by flash chromatography (SiO<sub>2</sub>, 5-10% MeOH/CHCl<sub>3</sub>) to give the title compound  
25 (0.065 g) mp 148-151°C.

Prepared similarly was:

Example 4

30

endo-N-(9-Methyl-9-aza-3-azabicyclo[3.3.1]nonan-7-yl)-4-  
amino-3,5-dichloro-2-methoxybenzamide (E4)

mp 170-172°C.

35

Example 5

endo-4-Amino-5-chloro-3-fluoro-2-methoxy-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)benzamide (E5)

5

The title compound was prepared from 4-amino-5-chloro-3-fluoro-2-methoxybenzoic acid via an analagous procedure to that described for Example 1.

10 The product was isolated as the hydrochloride salt, mp 202-203°C.

<sup>1</sup>H NMR (free base), (CDCl<sub>3</sub>), 250 MHz

15 δ: 8.61 (bd, 1H), 7.81 (d, 1H), 4.34 (bs, 2H), 4.20 (dd, 1H), 3.98 (d, 3H), 3.10 (b, 2H), 1.53-2.21 (m, 11H inc.s, 2.21, 3H).

20

5-HT<sub>3</sub> Receptor Antagonist Activity

Compounds are evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised  
25 rat according to the following method:

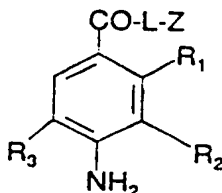
Male rats 250-350g, are anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate are recorded as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose  
30 of 5-HT (usually 6µg/kg) is given repeatedly by the intravenous route and changes in heart rate quantified. Compounds are given intravenously and the concentration required to reduce the 5-HT-evoked response to 50% of the  
35 control response (ED<sub>50</sub>) is then determined.

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:

5

10



(I)

wherein

R<sub>1</sub> is hydrogen or C<sub>1-6</sub> alkoxy;

15 R<sub>2</sub> is halo;

R<sub>3</sub> is halo;

L is O or NH; and

Z is a di-azacyclic or azabicyclic side chain;  
having 5-HT<sub>3</sub> receptor antagonist activity.

20

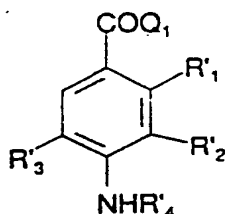
2. A compound according to claim 1 wherein R<sub>1</sub> is hydrogen,  
R<sub>2</sub> is chloro and R<sub>3</sub> is chloro.

3. A compound according to claim 1 wherein R<sub>1</sub> is methoxy,  
25 R<sub>2</sub> is fluoro or chloro and R<sub>3</sub> is chloro.

4. A compound according to any one of claims 1 to 3  
wherein the side chain Z is tropane, granatane,  
oxa/thia/aza-granatane, quinuclidine, isoquinuclidine,  
30 isogranatane, oxa/thia-isogranatane or isotropane.

5. A compound according to claim 4 wherein Z is tropane,  
oxagranatane or azagranatane.

6. A compound according to any one of claims 1 to 5 wherein L is NH.
7. **endo**-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-amino-3,5-dichlorobenzamide.
8. N-(1-Azabicyclo[2.2.2]octan-3-yl)-4-amino-3,5-dichlorobenzamide.
- 10 9. **endo**-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-amino-3,5-dichloro-2-methoxybenzamide.
10. **endo**-N-(9-Methyl-9-aza-3-azabicyclo[3.3.1]nonan-7-yl)-4-amino-3,5-dichloro-2-methoxybenzamide.
- 15 11. **endo**-4-Amino-5-chloro-3-fluoro-2-methoxy-N-(8-methyl-8-azabicyclo[3.2.1.]octan-3-yl)benzamide.
12. A pharmaceutically acceptable salt of a compound
- 20 according to any one of claims 7 to 11.
13. A compound according to claim 1 substantially as defined herein with reference to the Examples.
- 25 14. A process for the preparation of a compound according to claim 1, which process comprises reacting a compound of formula (II):



(II)

with a compound of formula (III):

HLZ'

(III)

or a reactive derivative thereof, when L is O;

5 wherein  $R_1'$ ,  $R_2'$ ,  $R_3'$  and/or  $Z'$  are  $R_1$ ,  $R_2$ ,  $R_3$  and/or  $Z$  respectively or groups or atoms convertible thereto;  $R_4$  is hydrogen or an N-protecting group;  $Q_1$  is a leaving group; and the remaining variables are as defined in claim 1; and  
10 thereafter optionally converting  $R_1'$ ,  $R_2'$ ,  $R_3'$  and/or  $Z'$  to another group or atom  $R_1$ ,  $R_2$ ,  $R_3$  or  $Z$ ; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

15 15. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

16. A method of treatment or prophylaxis of pain, emesis,  
20 CNS disorders and/or gastrointestinal disorders in mammals, such as humans, which comprises the administration of an effective amount of a compound according to claim 1.

17. A compound according to any one of claims 1 to 13 for  
25 use as an active therapeutic substance.

18. A compound according to any one of claims 1 to 13 for use in the treatment of pain, emesis, CNS disorders and/or gastrointestinal disorders.

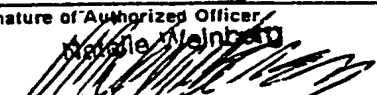
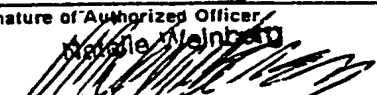
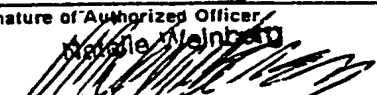
30

19. The use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the treatment and/or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders.

35

# INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/02210

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup> According to International Patent Classification (IPC) or to both National Classification and IPC <b>IPC5: C 07 D 451/04, 453/02, 498/08</b>														
<b>II. FIELDS SEARCHED</b> <div style="text-align: right; margin-right: 100px;">Minimum Documentation Searched<sup>7</sup></div> <table style="width: 100%; border: none;"> <tr> <td style="width: 20%; border: none;">Classification System</td> <td style="border: none;">Classification Symbols</td> </tr> <tr> <td style="border: none; height: 40px; vertical-align: bottom;">IPC5</td> <td style="border: none; vertical-align: bottom;">C 07 D</td> </tr> </table> <div style="text-align: center; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the extent that such Documents are included in Fields Searched<sup>8</sup></div>			Classification System	Classification Symbols	IPC5	C 07 D								
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<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category *</th> <th style="width: 60%;">Citation of Document,<sup>11</sup> with indication, where appropriate, of the relevant passages<sup>12</sup></th> <th style="width: 30%;">Relevant to Claim No.<sup>13</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">EP, A2, 0220011 (BEECHAM GROUP PLC) 29 April 1987, see compound 20  --</td> <td style="text-align: center; vertical-align: top;">1-15, 17-19</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">EP, A2, 0377967 (BEECHAM GROUP PLC) 18 July 1990, see example 2  --</td> <td style="text-align: center; vertical-align: top;">1-15, 17-19</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">EP, A1, 0099789 (DELALANDE S.A.) 1 February 1984, see especially compound 24  --</td> <td style="text-align: center; vertical-align: top;">1-15, 17-19</td> </tr> </tbody> </table>			Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	X	EP, A2, 0220011 (BEECHAM GROUP PLC) 29 April 1987, see compound 20  --	1-15, 17-19	X	EP, A2, 0377967 (BEECHAM GROUP PLC) 18 July 1990, see example 2  --	1-15, 17-19	X	EP, A1, 0099789 (DELALANDE S.A.) 1 February 1984, see especially compound 24  --	1-15, 17-19
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<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p><b>* Special categories of cited documents:<sup>10</sup></b></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p> </div> </div>														
<b>IV. CERTIFICATION</b> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;">           Date of the Actual Completion of the International Search   <b>10th March 1992</b> </td> <td style="width: 50%; border: none; vertical-align: top;">           Date of Mailing of this International Search Report   <div style="text-align: center;">6. 4. 1992</div> </td> </tr> <tr> <td style="width: 50%; border: none; vertical-align: top;">           International Searching Authority   <div style="text-align: center;"><b>EUROPEAN PATENT OFFICE</b></div> </td> <td style="width: 50%; border: none; vertical-align: top;">           Signature of Authorized Officer  <div style="text-align: center;">               Margarete Weinberg           </div> </td> </tr> </table>			Date of the Actual Completion of the International Search  <b>10th March 1992</b>	Date of Mailing of this International Search Report  <div style="text-align: center;">6. 4. 1992</div>	International Searching Authority  <div style="text-align: center;"><b>EUROPEAN PATENT OFFICE</b></div>	Signature of Authorized Officer <div style="text-align: center;">               Margarete Weinberg           </div>								
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	DE, DE, 3001328 (DELALANDE S.A.) 24 July 1980, see example 74  -----	1,4,14- 15,17- 19

## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE <sup>1</sup>

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ..... 16, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1 (iv: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☒ Claim numbers ..... 1-4\* because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The scope of the claims 1-4, 14-15, 17-19 is so broadly formulated that a very wide range of structures is included. These claims have thus not been fully searched.

\* 14-15, 17-19

3. ☐ Claim numbers..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING <sup>2</sup>

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 91/02210**

SA 53948

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on 01/02/92  
The European Patent office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0220011	29/04/87	AU-D- 6385586 JP-A- 62155277	16/04/87 10/07/87
EP-A2- 0377967	18/07/90	AU-D- 4608189 JP-A- 2202890	21/06/90 10/08/90
EP-A1- 0099789	01/02/84	AU-B- 562210 AU-D- 1650783 CA-A- 1265802 FR-A-B- 2529548 JP-A- 59021684 US-A- 4657911	04/06/87 05/01/84 13/02/90 06/01/84 03/02/84 14/04/87
DE-DE- 3001328	24/07/80	AU-B- 542537 AU-D- 5461080 BE-A- 881134 CA-A- 1130286 CA-A- 1160227 CH-A- 646969 CH-A- 647520 FR-A-B- 2446823 FR-A-B- 2476088 GB-A-B- 2042522 GB-A-B- 2055374 JP-C- 1333568 JP-A- 55108871 JP-A- 56164187 JP-A- 59076084 JP-B- 60059915 LU-A- 82083 NL-A- 8000277 NL-A- 8005774 SE-B-C- 431984 SE-B-C- 444941 SE-A- 8000068 US-A- 4321378 US-A- 4329466 US-A- 4424358 US-A- 4471120 US-A- 4536580	28/02/85 24/07/80 14/07/80 24/08/82 10/01/84 28/12/84 31/01/85 14/08/80 21/08/81 24/09/80 04/03/81 28/08/86 21/08/80 17/12/81 28/04/84 27/12/85 10/09/81 18/07/80 30/01/81 12/03/84 20/05/86 17/07/80 23/03/82 11/05/82 03/01/84 11/09/84 20/08/85

For more details about this annex : see Official Journal of the European patent Office, No. 12/82